<Division of Biochemistry> Chemical Biology

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- Chemical Biology -

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Visitors

Assist Prof KWON, Youngjoo	Ewha Womans University College of Pharmacy, Korea, 18 July–18 August 2006
Assoc Prof TAUNTON, Jack	University of California, San Francisco of Cellular & Molecular Pharmacology, USA, 26 July 2006
Prof CHOO, Hea-Young	Ewha Womans University College of Pharmacy, Korea, 12 October–12 December 2006
Prof MUIR, Thomas	Rockefeller University of Biochemistry and Structural Biology, USA, 9 September 2006

Scope of Research

In human history, small organic molecules have been utilized for improving human health and for revealing secrets of life. Discovery or design of small organic molecules with unique biological activity permits small-molecule-initiated exploration of biology and further understanding of human diseases. Our laboratory has been discovering small organic molecules that modulate transcription or differentiation to use them as tools to explore biology. Such chemistry-initiated biology is recently called chemical biology, an emerging field of biology and medical sciences. Although our chemical biology is a basic one, it may "catalyze" future drug discovery.

Research Activities (Year 2006)

Presentations

Chemical Biology of Gene Expression and Cell Differentiation, Uesugi M, Aging and Cancer Genome Research Work Shop, Sendai, Japan, 20 January 2006.

Chemical Biology by Small Synthetic Compounds, Uesugi M, 7th Drug Discovery Vision Symposium, Tokyo, Japan, 23 February 2006.

Chemical Biology of Gene Expression and Cell Differentiation, Uesugi M, 86th Annual Meeting of the Chemical Society of Japan, 27 March 2006.

Chemical Biology of Gene Expression and Cell Differentiation, Uesugi M, 126th Annual Meeting of the Pharmaceutical Society of Japan, 29 March 2006.

Chemical Biology of Gene Expression and Cell Differentiation, Uesugi M, ICOB-5 & ISCNP-25 IUPAC, Kyoto, Japan, 27 July 2006.

Chemical Biology by Small Synthetic Compounds, Uesugi M, Genomic Drug Discovery Forum, Kyoto, Japan, 19 September 2006.

Chemical Biology by Small Synthetic Compounds, Uesugi M, JSPS Genome Technology Symposium, Tokyo, Japan, 26 September 2006.

Chemical Biology of Gene Expression and Cell Differentiation, Uesugi M, Senri Life Science Seminar, Osaka, Japan, 29 September 2006.

Chemical Biology by Small Synthetic Compounds, Uesugi M, 2nd Forum for Pharmaceutical Technology Innovation, Kyoto, Japan, 13–14 October 2006.

Chemical Biology of Gene Expression and Cell Differentiation, Uesugi M, 21st International Biohybrid Symposium, Yokohama, Japan, 1 November 2006.

Chemical Biology of Gene Expression, Uesugi M, 43th

Small-molecule-initiated Biology

Knowledge about bioactive small molecules is a treasure of the humankind. Small organic compounds that the human being have discovered or synthesized from natural resources have been utilized for improving human health and for revealing secrets of life. The major goal of our research programs has been to expand the treasure by discovering and analyzing novel organic compounds with unique biological activities and to use them as tools to explore biology.

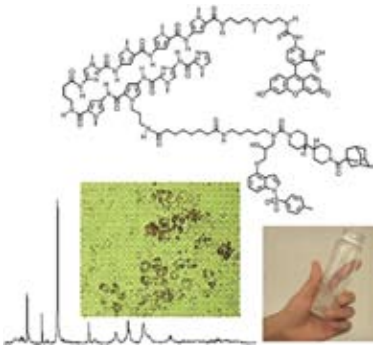
Our current research programs focus on discovering and using small organic molecules that modulate gene transcription or cell signaling. Regulation of gene transcription and cell signaling often induces drastic phenotypic changes in living organisms. Precise, external control over these endogenous processes through small organic molecules represents a challenge of chemistry to nature. The latest achievements are summarized below.

Discovery of synthetic small molecules that modulate transcription. Our group has discovered by screening chemical libraries a unique small-molecule modulator of transcription. The synthetic molecule we named "adamanolol" represents the first small molecules that modulate gene transcription by targeting transcription factor-coactivator interaction. Our group, as a collaboration with another laboratory, synthesized adamanolol and its derivatives and obtained structure-activity relationship, which enabled the design of the second-generation compound named "wrenchnolol." The wrench-shaped compound is now recognized in the field as a highly unique synthetic molecule that controls gene expression.

Wrenchnolol mimics an alpha-helical activation domain of transcription factor ESX: it may serves as a small-molecule activation module when coupled with a DNA binding molecule. Our group, as a collaboration with Prof. Dervan in Caltech, has recently succeeded in designing a completely organic, synthetic transcription factor that activates transcription. This work demonstrates that it is possible to generate a transcription factor out of organic compounds.

Discovery of small molecules that modulate cell signaling. Our group has developed an interesting method of screening chemical libararies for the discovery of bioactive molecules. In this unique method, synthetic small molecules were first profiled by their effects on phenotypic fat cell differentiation and pre-selected for more focused secondary assays. This approach enebled us to discover a number of bioactive compounds with a range of biological activities, including anti-proliferation of selective cell types and inhibition of lipogenesis. These molecules are now used for elucidation of new biological pathways in our group. For example, we recently discovered a new signaling pathway to control insulin/IGF pathways by utilizing the compound we call chromeceptin.

Our group also discovered small organic molecules that differentiate mouse embryonic stem (ES) cells into dopaminergic neurons. Our approach to discovering such molecules is rooted in the logic of asymmetric catalysts in chemistry. This work might be a good demonstration of applying the logic in chemistry to the biological field.



International JPS · PEM4, Yokohama, Japan, 6 November 2006.

Chemical Biology by Small Synthetic Compounds, Uesugi M, 3rd Combinatorial Bioengineering Conference, Osaka, Japan, 10 November 2006.

Grants

Uesugi M, Small-molecule Initiated Analysis of Cellular Signaling, Grant-in-Aid for Scientific Research (B), 1 April 2006–31 March 2008.

Kawazoe Y, Small Molecules That Modulate Cell Differentiation, Grant-in-Aid for Young Scientists (B), 1 April 2006–31 March 2008.

Uesugi M, Methods for Isolating Target Proteins of Small Molecules, Grant-in-Aid for Scientific Research on Priority Areas, 1 April 2006–31 March 2008.

Uesugi M, Intracellular Imaging of Small Molecules, Industrial Technology Research Grant Program by NEDO, 1 June 2006–20 March 2008.

Uesugi M, Small Molecule Transcription Factors for Biological Investigations, PRESTO, Japan Science and Technology Agency, 1 October 2005–31 March 2009.

Award

Uesugi M, Tokyo Techno-Forum 21Gold Medal Award, Small-molecule Based Chemical Genetic Research for Biological Investigation, 12 April 2006.